IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Hans Josef Stauss and Liquan Gao		
Serial No.:	09/625,963	Art Unit:	1644
Filed:	July 26, 2000	Examiner:	Francois P. Vandervegt
For:	*IMMUNOTHERAPEUTIC METHODS USING EPITOPES OF WT-1 AND GATA-1*		

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1, 5, 7, 15 and 19 in the Office Action mailed June 2, 2006, in the above-identified patent application. A Notice of Appeal was filed on August 24, 2006. This Appeal Brief is accompanied by a Petition for a One Month Extension of Time, extending the term for response to an including November 24, 2006. The Commissioner is hereby authorized to charge $500.00, the fee for the filing of this Appeal Brief for a large entity, and $120, the fee for the Petition for a One Month Extension of time as a large entity to Deposit Account No. 50-3129. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is Ganymed Pharmaceuticals AG, as assignee of the entire interest and SmithKline Beecham Corporation (doing business as GlaxoSmithKline) as a licensee.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS

Claims 5, 7, 15 and 19 are pending and appealed. Claims 1-4, 6, 8-14, 16-18, and 20-48 have been cancelled. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended in an Amendment and Response filed on March 13, 2006. An office action finally rejecting the claims was mailed on June 2, 2006. No amendment was filed after the mailing of the final rejection.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

Claim 1 defines a peptide derived from the amino acid sequence of human WT-1 polypeptide having at least 9 but fewer than 100 amino acids, wherein the peptide comprises the amino acid sequence RMFPNAPYL (SEQ ID NO:1)[1], and wherein the peptide is processed by

[1] RMFPNAPYL (SEQ ID NO:1) is also referred to in the specification as the "WT126-134" peptide, so-named

HLA-A0201-positive antigen presenting cells (APC) to produce the HLA-A0201 bound RMFPNAPYL (SEQ ID NO:1) sequence. Basis for claim 1 is found in the specification as originally filed, for example, at page 3, lines 11-27; page 6, lines 20-24; page 7, line 15; page 42, lines 1-13; page 43, lines 2-5; and page 56, lines 1-9.

Claim 5 depends from claim 1, and further defines the peptide as processed by HLA-A0201-positive antigen presenting cells (APC) to produce the sequence RMFPNAPYL (SEQ ID NO:1) that is capable of eliciting the production of a cytotoxic lymphocyte (CTL), wherein the CTL recognizes a HLA-AA0201-positive cell which aberrantly expresses intact human WT-1 protein. Basis for claim 5 is found in the specification as originally filed, for example at page 3, lines 11-18; page 8, lines 15-24; and page 60, line 18 to page 61, line 10.

Claim 7 depends from claim 1, and requires the amino acid sequence to be RMFPNAPYL (SEQ ID NO:1). Basis for claim 1 is found in the specification as originally filed, for example at page 3, lines 11-27; page 42, lines 1-13; page 43, lines 2-5; and page 56, lines 1-9.

Claim 15 defines a pharmaceutical composition comprising the peptide of claim 1 and a pharmaceutically acceptable carrier. Basis for claim 15 is found in the specification as originally filed, for example, at page 19, lines 15-25.

Claim 19 defines a vaccine for a tumor cell in which HLA-A0201 is expressed and WT-1 is over-expressed, wherein the vaccine comprises a peptide according to claim 1. Basis for claim 19 is found in the specification as originally filed, for example, on page 20, line 21 to page 23, line 27.

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because RMFPNAPYL are the amino acids found at positions 126-134 in the intact WT1 protein. See the

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues presented on appeal are:

(1) whether claims 1, 5, 7, 15 and 19 satisfy the written description requirement as required by 35 U.S.C. § 112, first paragraph.

(7) ARGUMENT

(a) Rejections under 35 U.S.C. § 112, first paragraph, written description

Claims 1, 5, 15 and 19 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention.

Claim 7 was objected to as dependent upon a rejected base claim.

Legal Standard

Compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, is a question of fact and must be assessed on a case-by-case basis. *Vas-Cath Inc. v. Marhurkar*, 935 F.2d 1555, 1561, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). It is settled law that the original disclosure of a patent application need not describe the claimed subject matter in issue in *haec verba*. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570, 29 USPQ2d 1895, 1904 (Fed. Cir. 1996). However, the original disclosure of the patent application must convey with reasonable clarity to those skilled in the art that the inventor was in possession of the invention now claimed. *Vas-Cath Inc.*, 935 F.2d at 1563-64, 19 USPQ2d at 1116-17. In other words, one skilled in the art

specification , e.g., at page 42, line 6 or page 56, lines 1-2.

must reasonably discern the claim limitation at issue from reading the original disclosure of the patent application. *Waldemar Link GMBH & Co. v. Osteonics Corp.*, 32 F.3d 556, 558, 31 USPQ2d 1855, 1857 (Fed. Cir. 1994). It is the examiner's initial burden to present evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976).

The Federal Circuit expressly stated in *Falkner v. Inglis*, 448 F.3d 1357, 79 USPQ2d 1001 (Fed. Cir. 2006) that there is no *per se* rule that an adequate written description of the invention that involves a biological molecule must contain recitation of known structure. The Court also affirmed that

> The descriptive text needed to meet these [written description] requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science. *Falkner* at 1367-1368 (Fed. Cir. 2006) *citing Capron v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005).

Although the structure discussed in *Falkner* concerned known DNA sequences, the rationale applied by the Court is even more applicable to amino acid sequences given the well characterized structure, programs for analysis and modification.

Analysis

Claim 1 Satisfies the Written Description Requirement

Claim 1 defines a peptide derived from the amino acid sequence of human Wilm's Tumor gene product ("WT-1") polypeptide, having at least 9 but fewer than 100 amino acids, comprising the sequence of SEQ ID NO:1, and which is processed by HLA-A0201-positive antigen presenting cells to produce the HLA-A0201 bound peptide of SEQ ID NO:1 (In the specification, SEQ ID NO:1 is also referred to as p126 peptide or WT126-34 peptide.).

As an initial matter, Applicants note that the amino acid sequence of full-length human WT1 was published prior to the filing date of the present application. Page 3, lines 5-9 of the specification disclose that the amino acid sequence encoded by the Wilm's Tumor gene was published in U.S. Patent No. 5,726,288 (issued 10 March 1998). Page 8, lines 9-13 of the specification disclose that the amino acid sequence for WT-1 is also given in Gessler et al. (1990) *Nature*, **343**, 774-778. The Court of Appeals for the Federal Circuit has unequivocally held that there is no *per se* rule that an adequate written description of the invention that involves a biological molecule must contain recitation of known structure. *Falkner v. Inglis*, 448 F.3d 1357, 79 USPQ2d 1001 (Fed. Cir. 2006). Therefore, the entire amino acid sequence of known proteins is not required to be a part of the specification to satisfy the written description requirement.

The present inventors identified SEQ ID NO:1 as a natural Cytotoxic T Lymphocyte (CTL) epitope (see Example 1). CTLs raised against a peptide comprising SEQ ID NO:1 were shown to kill tumor cells expressing WT-1 (see, pages 42-43, Figures 1 and 2). Such CTLs were produced using the method described in Example 2, using HLA-A2 antigen presenting cells and a peptide of SEQ ID NO:1.

Appellants submit that Claim 1 meets the written description requirement because each element of claim 1 is described in the specification. For example, SEQ ID NO:1 is disclosed in the specification at least at page 3, lines 25-27 and page 9, lines 12-14. Page 7, lines 10-15, of the specification disclose that the peptide can be fewer than 100 residues. Page 9, lines 9-10, disclose that the peptide can be 9 amino acids in length. Lines 20-22 of page 9 disclose that larger of the claimed peptides can be fragmented by suitable antigen-presenting cells. Page 3, lines 11-18, disclose that the present inventors identified peptide epitopes including SEQ ID NO:1, can be presented by HLA-A0201 class molecules. Page 6, lines 9-12, disclose that the peptides may be processed by an antigen presenting cell so that a fragment is produced that binds to an appropriate MHC I molecule.

In the Final Office Action dated 2 June 2006, the Examiner states that, other than the 9-amino acid peptide of SEQ ID NO:1, the specification does not teach:

1) the sequence of any other peptide comprising 9-100 amino acids and having the amino acid sequence of SEQ ID NO:1 contained therein

2) the identity of residues which constitute the cleavage sites for the processing by HLA-A0201 APCs to produce the peptide of SEQ ID NO:1 as recited in the claims, or

3) the identity of any enzyme that would facilitate the cleavage of the claimed 9-100 amino acid peptide into the HLA-0201 identifiable sequence of SEQ ID NO:1 (Final Office Action, 2 June 2006, page 3-4).

The Examiner concludes that "the single species disclosed in the specification does not provide an adequate written description of the entire genus to show that it was indeed in Applicant's possession…" (*Id.*)

The Examiner alleges that one species is insufficient to support the claimed genus. The specification discloses that the claimed peptide can be a truncated WT-1 protein (*Id.*). As noted above, the amino acid sequence for WT-1 was known in the art (page 8, lines 9-13); the claimed peptides are fragments of WT-1 of fewer than 100 amino acids but comprising the 9 amino acid sequence found at residues 126-136 of WT-1. Appellants submit that, given this description, the specific amino acid sequence of a plurality of the truncated proteins need not be explicitly stated in the specification to satisfy the written description requirement.

As stated in *University of California v. Eli Lilly and Co.*:

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus **or** of a

> recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.

University of California v. Eli Lilly and Co., 119 F. 3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) citing *In re Grimme* , 274 F. 2d 949, 952, 124 USPQ 499 (CCPA 1960) (" [I]t has been consistently held that the naming of one member of such a group is not, in itself, a proper basis for a claim to the entire group. However, it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by 'other appropriate language.' ") (emphasis added and citations omitted).

The Final Office Action states that "adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it", citing *Fiers v. Revel*, 984 F.2d 1167, 1171, 25 USPQ2d 1601 (Fed. Cir. 1993). Appellants submit that the Examiner's reliance on *Fiers* is misplaced in the present instance. In *Fiers*, the written description was found insufficient where the patent claimed purified DNA encoding a human fibroblast polypeptide, but the specification only disclosed a reference to the DNA and suggested a process to sequence it. The Federal Circuit, discussing *Fiers*, has stated:

> (T)he patent specifications at issue [in *Fiers*] did not identify the sequence (structure) of <u>any</u> embodiment of DNA claimed therein. …. In contrast, the shared written description for the patents-in-issue recites both the DNA and amino acid sequences of a representative embodiment of the claimed RT enzyme. The specification also discloses test data that the enzyme produced by

> the listed sequence has the claimed features—DNA polymerase activity without RNase H activity. Under both the *Eli Lilly* and *Fiers* analysis, the specification at bar is sufficient.

Invitrogen v. Clontech, 429 F.3d 1052, 77 USPQ2d 1161, 1176 (Fed. Cir. 2006) (emphasis added).

Appellants submit that the present specification, considered as a whole, provides adequate written description of the claimed subject matter. The sequence of a representative embodiment of the claimed invention is provided (SEQ ID NO:1); the specification also discloses experimental data indicating that this peptide has the claimed functional features. All members of the claimed genus share a common structural feature: they comprise the RMFPNAPYL sequence (SEQ ID NO:1), which is shown in the present specification to be a CTL epitope. Further, the members of the claimed genus share the functional features recited in the claims.[2]

The Examiner further alleges that claim 1 does not satisfy the written description requirement because the identity of the residues which constitute the cleavage sites of the peptide for processing by the HLA-A0201 antigen presenting cells is not disclosed. The claims do not require a specific cleavage site. The claims require that the peptide be processed by an HLA-A0201 positive antigen presenting cell into HLA-A0201 bound peptide. Appellants submit that, using the information known in the art and provided in the present specification, one skilled in

[2] Additionally, the specification provides written description for other peptides including gata-1 peptides such as SEQ ID NO:3.

the art would be able to determine which fragments of WT-1 of at least 9 but fewer than 100 amino acids are so processed. The specification discloses that it was known in the art that antigen presenting cells, for example dendritic cells, take up exogenous antigen, process it and present it to cytotoxic T cells (paragraph bridging pages 48-49). Thus, claim 1 satisfies the written description requirement.

The Examiner also alleges that claim 1 fails to satisfy the written description requirement because the identity of the enzyme that would facilitate cleavage of the claimed peptide into SEQ ID NO:1 is not disclosed. The claims do not require that the peptide be cleaved by a specific enzyme. Therefore, the identification of a specific enzyme is not required to satisfy the written description requirement. The necessary amount of written description varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The specification discloses that the entire amino acid sequence of WT-1 was known in the art, and that dendritic cells process exogenous antigen into fragments and display the antigen to CTLs. The specification describes that the WT-1 fragment of SEQ ID NO:1 is processed by HLA-A0201 antigen presenting cells, displayed on the surface of the cell, and capable of stimulating Cytotoxic T Lymphocytes. In view of this disclosure, one of skill in the art would recognize that the inventors were in possession of the claimed subject matter at the time the application was filed.

Claim 5 Satisfies the Written Description Requirement

Claim 5 depends from claim 1 and requires that the peptide be capable of eliciting the production of cytotoxic lymphocyte, wherein the CTL recognizes HLA-A0201-positive cell

which aberrantly expresses intact human WT-1 protein. Example 1 beginning on page 39 discloses the identification of the RMFPNAPYL (SEQ ID NO:1) fragment of as a natural CTL epitope. Page 43, lines 2-3 disclose that CTLs against the WT126-34 peptide (SEQ ID NO:1) kill tumor cells expressing HLA-A0201 and WT-1. Therefore, claim 5 satisfies the written description requirement.

Claim 7 Satisfies the Written Description Requirement

Claim 7 depends from claim 1 and specifically requires that the peptide have the sequence of SEQ ID NO:1. SEQ ID NO:1 is disclosed in the specification at least at page 3, lines 25-27; and page 9, lines 12-14. Therefore, claim 7 satisfies the written description requirement.

Claim 15 Satisfies the Written Description Requirement

Claim 15 defines a pharmaceutical compound comprising the peptide of claim 1. Claim 1 satisfies the written description requirement for the reasons provided above. The specification discloses pharmaceutical compositions containing the claimed peptides at page 19, lines 15-25. The pharmaceutical compositions can include a pharmaceutically acceptable carrier (*Id.*) Thus, claim 15 satisfies the written description requirement.

Claim 19 Satisfies the Written Description Requirement

Claim 19 defines a vaccine comprising the peptide of claim 1, for use against a tumor cell in which HLA-A0201 is expressed. Claim 1 satisfies the written description requirement for the reasons discussed above. The specification discloses vaccines comprising the claimed peptide at

page 20, line 24 to page 24, line 21 and page 66, lines 8-12. Thus, claim 19 satisfies the written description requirement.

(8) SUMMARY AND CONCLUSION

Appellants submit that the claimed genus of peptides is supported by an adequate written description, as the members of the claimed genus share both structure (SEQ ID NO:1) and function, and the claimed structure and functions are disclosed in the specification. The peptide of SEQ ID NO:1, as claimed in claim 7, provides one embodiment of the claimed genus.

Further, the Court of Appeals for the Federal Circuit has unequivocally held that there is no *per se* rule that an adequate written description of the invention that involves a biological molecule must contain recitation of known structure. *Falkner v. Inglis*, 448 F.3d 1357, 79 USPQ2d 1001 (Fed. Cir. 2006). The present specification discloses that the amino acid sequence for WT-1 was known in the art prior to the filing of the application.

Claim 1 satisfies the written description requirement because the specification discloses WT-1 peptides comprising SEQ ID NO:1 and that the peptides are truncated WT-1 protein fragments. The specification also discloses that the peptides can be fewer than 100 amino acids and at least 9 amino acids.

Claim 5 satisfies the written description requirement because the specification discloses that the peptide is capable of eliciting the production of cytotoxic lymphocytes, wherein the CTL recognizes an HLA-A0201-positive cell which aberrantly expresses intact human WT-1 protein (Example 1 beginning on page 39).

Claim 7 satisfies the written description requirement because SEQ ID NO:1 is disclosed throughout the specification.

Claim 15 satisfies the written description requirement because the specification discloses pharmaceutical compositions including pharmaceutically acceptable carriers containing the claimed peptides at page 19, lines 15-25

Claim 19 satisfies the written description requirement because the specification discloses vaccines comprising the claimed peptide at page 20, line 24 to page 24, line 21.

For the foregoing reasons, Appellant submits that the specification provides adequate written description for claims 1, 5, 7, 15, and 19 are patentable.

Respectfully submitted,

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Claims Appendix: Claims On Appeal

1. A peptide derived from the amino acid sequence of human WT-1 polypeptide having at least 9 but fewer than 100 amino acids, wherein the peptide comprises the amino acid sequence RMFPNAPYL (SEQ ID NO:1), and wherein the peptide is processed by HLA-A0201-positive antigen presenting cells (APC) to produce the HLA-A0201 bound RMFPNAPYL (SEQ ID NO:1) sequence.

5. A peptide according to claim 1 wherein the peptide is processed by HLA-A0201-positive antigen presenting cells (APC) to produce the sequence RMFPNAPYL (SEQ ID NO:1) that is capable of eliciting the production of a cytotoxic lymphocyte (CTL), wherein the CTL recognizes a HLA-A0201-positive cell which aberrantly expresses intact human WT-1 protein.

7. A peptide according to claim 1 consisting of the amino acid sequence RMFPNAPYL (SEQ ID NO:1).

15. A pharmaceutical composition comprising the peptide of claim 1 and a pharmaceutically acceptable carrier.

19. A vaccine for a tumor cell in which HLA-A0201 is expressed and WT-1 is over-expressed comprising a peptide according to claim 1.

Evidence Appendix

None.

Related Proceedings Appendix

None.